ATTACHMENT B

DERIVATION OF A REFERENCE CONCENTRATION (RfC) FOR
N-PROPYL BROMIDE (NPB)

ICF has performed an evaluation of the literature on n-propyl bromide (1-bromopropane, NPB) for the purpose of evaluating its potential metabolites and their expected toxicity following inhalation exposure. The toxicity data reviewed for this study consisted of a two-generation inhalation study (WIL 2001) and one 13-week inhalation study in rats (ClinTrials 1997). ICF has derived an Acceptable Exposure Limit (AEL) for workplace exposures in a separate document (Derivation of an AEL for NPB, ICF 2002). Using the same database, ICF derived an RfC for NPB as a screening tool to assess risk to the general population including sensitive individuals such as children and the elderly.

Recommended RfC: 1 ppm
Basis:

      Endpoints: Effects on sperm motility and liver effects

      Study: An Inhalation Two-Generation Reproductive Toxicity Study of 1-Bromopropane in Rats (WIL 2001)

      Protocol: Whole-body inhalation, 6 hours/day, 7 days/week

      Concentrations: 0, 100, 250, 500 or 750 ppm

      NOAEL: 100 ppm

      LOAEL: 250 ppm (spermatic and hepatic effects)

      $BMDL_{sperm\ effects}$ [adj.]: 169 ppm x 6 hours/24 hours = 40 ppm

      $BMDL_{sperm\ effects}$[HEC]: 40 ppm

      Uncertainty/
      Modifying Factors: 3 - animal to human extrapolation (pharmacodynamic differences)
      10 - sensitive individuals

      $RfC_{sperm\ effects}$: 1 ppm

      $BMDL_{liver\ effects}$ [adj.]: 110 ppm x 6 hours/24 hours = 28 ppm
      $BMDL_{liver\ effects}$ [HEC]: 28 ppm

      Uncertainty/
      Modifying Factors: 2 - animal to human extrapolation
      10 sensitive individuals

      $RfC_{liver\ effects}$: 1 ppm

An RfC for NPB was derived using the results of the benchmark dose modeling conducted on data sets from the WIL (2001) and ClinTrials (1997b) studies. The summary results of the benchmark modeling are presented in Table 1. As shown in Table 1, following the application of the selection criteria, BMDLs ranging from 110 to 312 ppm were identified. For the two effects of concern, the lowest BMDL values derived were 110 ppm for the incidence of liver vacuolation in the F_1 males, and 169 ppm for the effects on sperm motility in the F_1 generation of the two-generation study. For a full discussion on the development and selection of these BMDL values see Attachment A, Acceptable Exposure Limit for NPB (ICF, 2002).

RfCs were derived based on both hepatic and spermatic effects in order to determine the most conservative choice. The lowest BMDL of 110 ppm was based on the incidence of hepatocellular centrilobular vacuolation in F_1 males in the two-generation reproductive study (WIL 2001). Using EPA's RfC dosimetry guidelines for a category 3 gas (USEPA 1994) and making the appropriate adjustments to continuous exposure, the human equivalent concentration (HEC) is 110 ppm * (6 hours/24 hours) = 28 ppm. Because the blood/air partition for NPB in the human (7.1) is less than in the rat (11.7), no adjustment for differences in pharmacokinetics was necessary. An uncertainty factor of 2 was applied for animal to human extrapolation in consideration of potential differences in pharmacodynamics. Because *in vitro* data have indicated that human liver cells are no more sensitive to the effects of NPB than rat liver cells (Stelljes 2001), a full uncertainty factor of 3 for differences in pharmacodynamics was considered unnecessary. An uncertainty factor of 10 was applied for the protection of sensitive subpopulations (e.g., individuals with liver disease). Therefore, the total uncertainty factor was 20 (2 for differences in pharmacodynamics and 10 for the protection of sensitive individuals). The application of the uncertainty factor of 20 to the HEC (28 ppm) results in an RfC of 1 ppm.

The next lowest BMDL (169 ppm) was for the effects on sperm motility in the F_1 males (Table 1). In the derivation of an RfC for this endpoint, the BMDL was adjusted to continuous exposure as discussed above resulting in a HEC of 40 ppm. An uncertainty factor of up to 10 may be applied for animal-to-human extrapolation in consideration of potential differences in pharmacokinetics and pharmacodynamics. However, for the reasons listed above, a factor for differences in pharmacokinetics was not considered necessary. The results of the *in vitro* studies conducted with liver cells do not allow any conclusions to be drawn regarding the relative sensitivity of the human and rat spermatocyte to NPB. Consequently, a factor of 3 was applied for differences in pharmacodynamics. An uncertainty factor of 10 was applied for the protection of sensitive individuals. Uncertainty factors of up to 10 are typically applied when developing an RfC value unless there are data that lower values may be appropriate. It is important to note that the underlying assumptions used in developing an RfC, a value used to assess risk to the general population, differ from the assumptions used in developing occupational exposure levels. This is because the occupational environment is populated by individuals representing a healthy, adult population that does not include children or the elderly. Further, exposures in an occupational environment are limited, whereas exposures to the general population are assumed to occur continuously. In developing the occupational exposure limit, ICF used uncertainty factors ranging from 2-3 for protection of sensitive individuals in the workplace (e.g., men with low number of motile sperm). However, in order to develop an RfC that would protect for any potential effects of NPB on the reproductive health of children, the full uncertainty factor of 10 was considered necessary. Therefore, an overall uncertainty factor of 30 (3 for differences in pharmacodynamics and 10 for the protection of sensitive individuals) results. The application of the overall uncertainty factor to the HEC (40 ppm) results in an RfC of 1 ppm.

The estimated RfC values are identical for both hepatic and reproductive effects. Consequently, the recommended RfC is 1 ppm.

Table 1 SUMMARY OF BENCHMARK MODELING FOR NPB

Endpoint	Model	BMR	Risk Type	BMD	BMDL	Reference
Female						
Hepatocellular Centrilobular Vacuolation F_0 Female	Multistage	0.1	Extra	418.37	312.21	WIL 2001
Hepatocellular Centrilobular Vacuolation F_1 Female	LogProbit	0.1	Extra	302.24	209.39	WIL 2001
Male						
Hepatocellular Centrilobular Vacuolation F_0 Male	Loglogistic	0.1	Extra	187.64	143.49	WIL 2001
Hepatocellular Centrilobular Vacuolation F_1 Male	LogProbit	0.1	Extra	145.82	110.33	WIL 2001
Hepatocellular Centrilobular Vacuolation Male	Multistage	0.1	Extra	345.70	226.13	ClinTrials 1997b
Sperm Motility F_0 Males	Power	1.1	[a]	362.43	281.60	WIL 2001
Sperm Motility F_1 Males	Power	1.1	[a]	275.76	168.77	WIL 2001

[a]   Standard deviations from the control mean.